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TR/4 33714 P2

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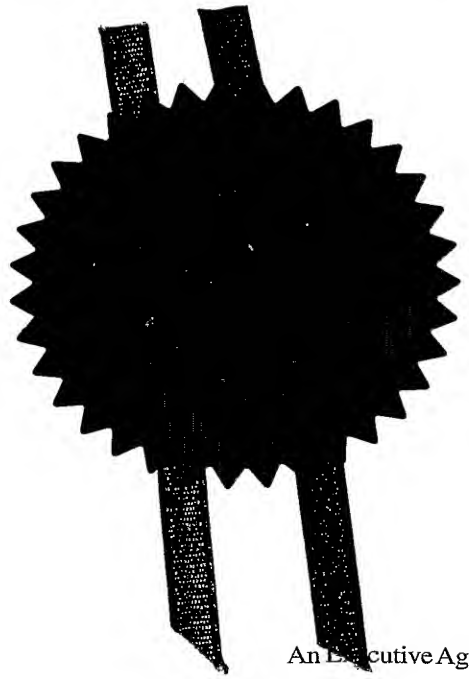

Signed Andrew Cay

Dated 24 January 2005

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1.	Your reference	4-33714P2
2.	Patent application number *(The Patent Office will fill in this part)*	29 JUN 2004 0414540.5
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)* 07125487005 Patent ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	Craig McLean Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB 07181522002 ✓

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

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Continuation sheets of this form	
Description	12
Claim(s)	5
Abstract	
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig McLean 29th June 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs S Schnerr 01403 323069

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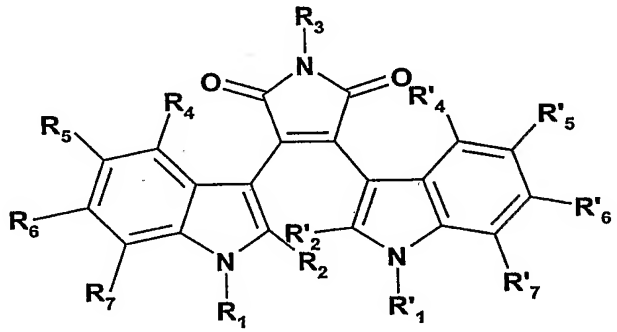
DUPLICATE

Organic Compounds

The present invention relates to new uses of protein kinase C inhibitors.

In particular, the present invention relates to new uses of protein kinase C inhibitors of formula I, II, III and IV and pharmaceutically acceptable salts or solvates thereof.

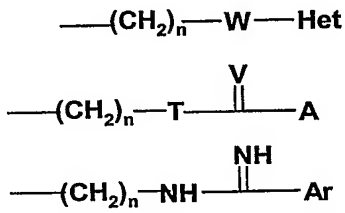
Protein kinase C inhibitors of formula I are as follows:



I

wherein

each of R_1 and R'_1, independently, is hydrogen, alkyl, haloalkyl, alkenyl, arylalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, acylaminoalkyl, acyloxyalkyl, cyanoalkyl, amidinoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, or a group of the formula (a), (b) or (c)



(a)

(b)

(c)

wherein Het signifies a heterocyclyl group; W signifies NH, S or a bond; T signifies NH or S; V signifies O, S, NH, or NCN; A signifies alkylthio, amino, monoalkylamino or dialkylamino; Ar signifies aryl;

each of R_2 and R'_2, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, $S(O)C_1$–C_3alkyl, CF_3;

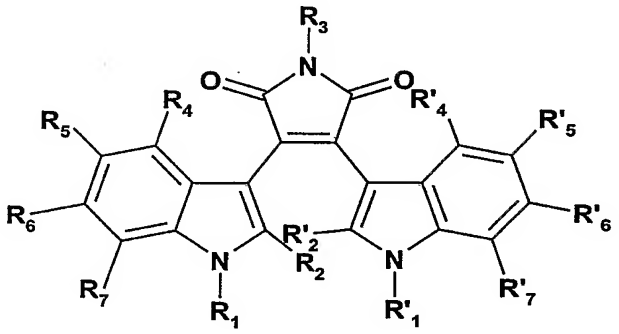
or R_1 and R_2 form together —$(CH_2)_r$—X—CH_2— wherein r is 1, 2, or 3, and X is CHR_8 or NR_8 wherein R_8 is $(CH_2)_sR_9$ wherein R_9 is hydrogen, hydroxy, alkoxy, amino, monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl, and s is 0, 1, 2 or 3;

R_3 is hydrogen or CH_3CO;

each of R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7 and R'_7, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, —COO(C_1–C_3alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_3alkylthio, or S(O)C_1–C_3alkyl; and

n is 1, 2, 3, 4, 5 or 6.

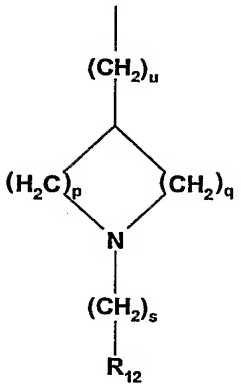
Protein kinase C inhibitors of formula II are as follows:



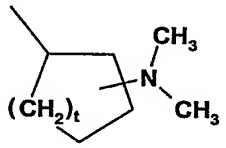
II

wherein

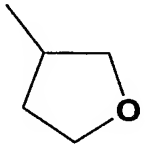
R_1 is a group of formula (d), (e) or (f)



(d)



(e)



(f)

wherein each of p and q independently is 1, 2, 3, or 4;

s is 0, 1, 2 or 3;

t is 1 or 2;

u is 0 or 1; and

R_{12} is hydrogen, alkyl, haloalkyl, cycloalkyl, acetyl, aryl, --CH(aryl)$_2$, amino, monoalkylamino, dialkylamino, guanidino, —C(=N(alkoxycarbonyl))NH(alkyoxycarbonyl), amidino, hydroxy, carboxy, alkoxycarbonyl or heterocyclyl;

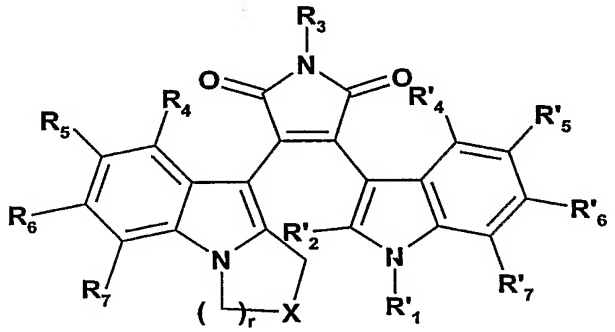
R'_1 is hydrogen, C_{1-4}alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl,

each of R_2 and R'_2, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, S(O)C_1–C_3alkyl, CF_3;

R_3 is hydrogen or CH_3CO—; and

each of R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7 and R'_7, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, --COO(C_1–C_3alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_3alkylthio, or S(O)C_1–C_3alkyl.

Protein kinase C inhibitors of formula III are as follows:



III

wherein

R'_1 is hydrogen, C_1-C_4alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R'_2 is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, S(O)C_1–C_3alkyl, CF_3

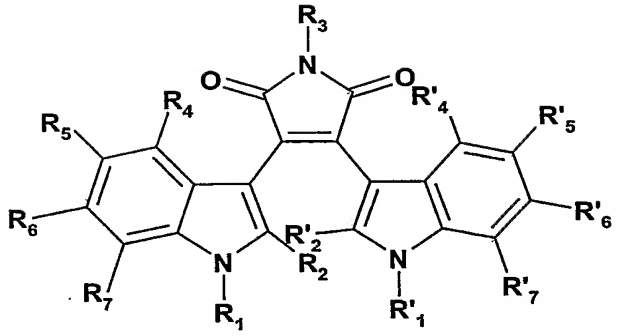
R_3 is hydrogen or CH_3CO—;

each of R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7 and R'_7, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, —COO(C_1–C_3alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_3alkylthio, or S(O)C_1–C_3alkyl;

X is CR_8R_9 wherein R_8 is $(CH_2)_sR_{10}$ wherein R_9 is $(CH_2)_sR_{11}$, each of R_{10} and R_{11}, independently, is hydroxy, alkoxy, carboxy, acyloxy, amino, monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl, and s is 0, 1, 2 or 3; and

r is 1, 2, or 3.

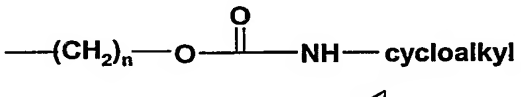
Protein kinase C inhibitors of formula IV are as follows:



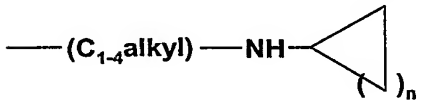
IV

wherein

R_1 is alkylglycose residue or a group of formula (g) or (h)



(g)



(h)

wherein n is 1, 2, 3, 4, 5 or 6;

R'_1 is hydrogen, C_1-C_4alkyl, cyclopropylmethyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

each of R_2 and R'_2, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, S(O)C_1–C_3alkyl, CF_3;

R_3 is hydrogen or CH_3CO—; and

each of R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7 and R'_7, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, --COO(C_1–C_3alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_3alkylthio, or S(O)C_1–C_3alkyl.

Alkyl, alone or in combinations, may be a straight or branched-chain alkyl group containing from 1 to 7, preferably 1 to 4, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl and pentyl. "C_1–C_3alkyl" is an alkyl limited to one to four carbon atoms. Alkenyl may be a 2 to 7 carbon, straight or branched hydrocarbon containing one or more double bonds, preferably one or two double bonds. Examples of alkenyl include ethenylene, propenylene, 1,3 butadienyl, and 1,3,5-hexatrienyl.

Cycloalkyl, alone or in combinations, may be a 3 to 7 carbon cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Alkoxy, alone or in combinations, may be an alkyl covalently bonded by an —O— linkage. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy. Alkoxyalkyl may be e.g. $CH_3(CH_2)$—O—$(CH_2)_m$ may be e.g. t-butoxycarbonyl or BOC.

Haloalkyl may be an alkyl with one or more, preferably 1 to 3 halogen atoms, e.g. CH_2Cl, CF_3, CH_2CF_3, $CH_2(CF_2)_2CF_3$, and the like.

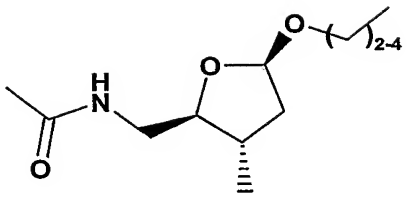
The acyl moiety of an acylamino or acylaminoalkyl group is derived from an alkanoic acid containing a maximum of 7, preferably a maximum of 4, carbon atoms, e.g. acetyl, propionyl or butyryl, or from an aromatic carboxylic acid, e.g. benzoyl. An acyloxy is one such acyl bonded by an —O— linkage e.g. acetyloxy, $CH_3C(=O)O$—. An acylamino is e.g. $CH_3(C=O)NH$—(acetylamino). Likewise, an acylaminoalkyl is CH_3 $(C=O)NH(CH_2)_m$—.

Aryl, alone or in combinations, may be an unsubstituted phenyl group or a phenyl group carrying one or more, preferably 1 to 3, substituents, independently selected from halogen, alkyl, hydroxy, benzyloxy, alkoxy, haloalkyl, nitro, amino, acylamino, monoalkylamino, dialkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl and cyano. Arylalkyl is preferably benzyl.

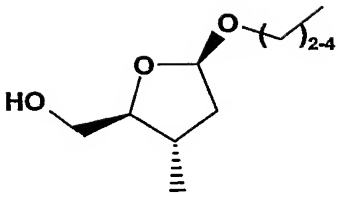
Halogen may be fluorine, chlorine, bromine or iodine.

The heterocyclic group denoted by "Het" or "heterocyclyl" may be a stable, saturated, partially unsaturated, or aromatic 5- or 6-membered heterocyclic group. The heterocyclic ring consists of carbon atoms and from 1 to 3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The heterocyclic group may optionally be substituted with 1 to 3 substituents independently selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, monoalkylamino, dialkylamino, alkylthio, alkylsulfinyl and alkylsulfonyl or, when the heterocyclyl group is an aromatic nitrogen-containing heterocyclic group, the nitrogen atom can carry an oxide group. Examples of such heterocyclyl groups include imidazolyl, imidazolinyl, thiazolinyl, pyridyl, indolyl, furyl, and pyrimidinyl.

"Alkylglycose residue" may be a glycose moiety linked in the C-1 position to the indolyl via a C_2-C_4alkyl. Glycoses included in alkylglycose residue are natural or unnatural 5 or 6 carbon sugars, preferably selected from allosyl, altrosyl, glucosyl, mannosyl, gulosyl, idosyl, galactosyl, talosyl, arabinosyl, xylosyl, lyxosyl, rhamnosyl, ribosyl, deoxyfuranosyl, deoxypyranosyl, and deoxyribosyl. The glycose may be azide substituted, O-acetylated, O-methylated, amino, mono- and di-alkylamino substituted, or acylamino substituted. For example, alkylglycose residue includes

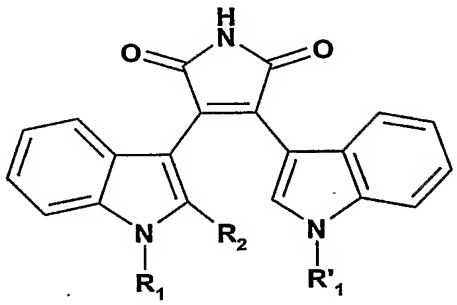


and



Particularly preferred protein kinase C inhibitors are compounds of formula Ia, Ib, IIa, and IIIa.

Compounds of formula Ia are as follows



Ia

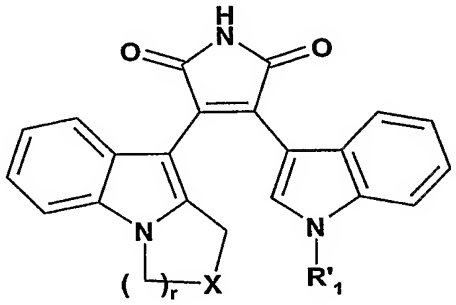
wherein

R_1 is hydrogen, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R'_1 is hydrogen, C_{1-4}alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl; and

R_2 is hydrogen or methyl.

Compounds of formula Ib are as follows



Ib

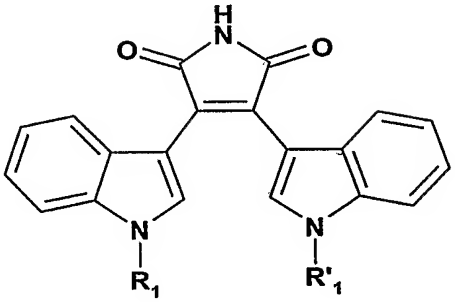
wherein

R'_1 is hydrogen, or C_1-C_4alkyl;

X is CR_8R_9 or NR_8 wherein R_8 is $(CH_2)_sR_{10}$ wherein R_9 is $(CH_2)_sR_{11}$, each of R_{10} and R_{11}, independently, is hydrogen, hydroxy, amino, monoalkylamino, or dialkylamino, and s is 1; and

r is 1 or 2.

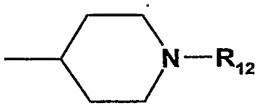
Compounds of formula IIa are as follows



IIa

wherein

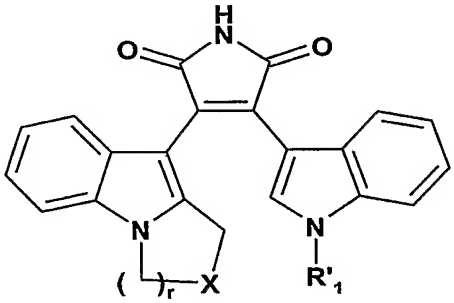
R_1 is



wherein R_{12} is hydrogen, or C_{1-4}alkyl; and

R'_1 is hydrogen, or C_{1-4}alkyl;

Compounds of formula IIIa are as follows:



IIIa

wherein

R'_1 is hydrogen, alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

X is CR_8R_9 or NR_8 wherein R_8 is $(CH_2)_sR_{10}$ wherein R_9 is $(CH_2)_sR_{11}$, each of R_{10} and R_{11}, independently, is hydroxy, carboxy, alkoxycarbonyl, amino, monoalkylamino, or dialkylamino, and s is 0 or 1; and

r is 1 or 2.

Even more preferred is 3-(1-methyl-1H-indol-3-yl)-4-[1-(1-pyridin-2-ylmethyl-piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, also called LY 317615 (Compound A hereinafter).

The compounds of formula I, II, II and IV may be synthesized as known in the art, e.g. as described in US 5,545,636.

Protein kinase C inhibitors of formula I, II, III or IV and pharmaceutically acceptable salts or solvates thereof have, on the basis of observed activity, e.g. inhibiting protein kinase C β-1 and β-2 isozymes, e.g. as described in US 5,545,636, been found to be useful in treating conditions associated with diabetes mellitus and its complications, as well as other diseases associated with an elevation of the β-1 and β-2 isozymes, e.g. ischemia, inflammation, central nervous system disorders, cardiovascular disease, dermatological disease, Alzheimer's disease, and cancer.

It has now been found that protein kinase C inhibitors of formula I, II, III or IV, e.g. of formula Ia, Ib, IIa and IIIa, and pharmaceutically acceptable salts or solvates thereof are useful for the treatment and prevention of organ, tissue or cell transplant rejection, e.g. for the treatment of recipients of solid organs or tissues, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants, or of cells, e.g. stem cells, or insulin-producing cells, e.g. pancreatic islet cells. They are also indicated for the prevention of graft-versus-host disease, such as following bone marrow transplantation.

In accordance with the particular findings of the present invention, there is provided a method for treating organ, tissue or cell transplant rejection, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplant rejection, and for preventing graft-versus-host disease in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a protein kinase C inhibitor of formula I, II, III or IV, e.g. of formula Ia, Ib, IIa and IIIa, or a pharmaceutically acceptable salt or solvate thereof.

Furthermore, it has now been found that protein kinase C inhibitors of formula I, II, III or IV, e.g. of formula Ia, Ib, IIa and IIIa, and pharmaceutically acceptable salts or solvates thereof are useful for the treatment and prevention of autoimmune diseases, in particular inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis; amyotrophic lateral sclerosis (ALS); multiple sclerosis; rheumatoid arthritis and hepatitis C.

Accordingly, the present invention provides a method for treating or preventing autoimmune diseases, in particular inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis; amyotrophic lateral sclerosis (ALS); multiple sclerosis; rheumatoid arthritis

and hepatitis C, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a protein kinase C inhibitor of formula I, II, III or IV, e.g. of formula Ia, Ib, IIa and IIIa, or a pharmaceutically acceptable salt or solvate thereof.

In the present description the terms "treatment" or "treat" refer to both prophylactic or preventive treatment as well as curative or disease modifying treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition.

In a series of further specific or alternative embodiments, the present invention also provides:

1. A protein kinase C inhibitor of formula I, II, III or IV or a pharmaceutically acceptable salt or solvate thereof for use in the methods as defined above.

2. A protein kinase C inhibitor of formula I, II, III or IV or a pharmaceutical acceptable salt or solvate thereof for use in the preparation of a pharmaceutical composition for use in the methods as defined above.

3. A pharmaceutical composition for use in the methods as defined above, comprising a protein kinase C inhibitor of formula I, II, III or IV or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable diluents or carriers therefore.

Utility of the compounds of the invention in treating and/or preventing diseases and conditions as hereinabove specified, may be demonstrated in standard animal or clinical tests, e.g. as described hereinafter.

In vivo: Rat Heart transplantation

The strain combination used: Male Lewis (RT^1 haplotype) and DA (RT^1 haplotype). The animals are anaesthetised using inhalational isofluorane. Following heparinisation of the donor rat through the abdominal inferior vena cava with simultaneous exsanguination via the aorta, the chest is opened and the heart rapidly cooled. The aorta is ligated and divided distal to the first branch and the brachiocephalic trunk is divided at the first bifurcation. The left pulmonary artery is ligated and divided and the right side divided but left open. All other vessels are dissected free, ligated and divided and the donor heart is removed into iced saline.

The recipient is prepared by dissection and cross-clamping of the infra-renal abdominal aorta and vena cava. The graft is implanted with end-to-side anastomoses, using 10/0 monofilament suture, between the donor brachiocephalic trunk and the recipient aorta and the donor right pulmonary artery to the recipient vena cava. The clamps are removed, the graft tethered retroabdominally, the abdominal contents washed with warm saline and the animal is closed and allowed to recover under a heating lamp. Graft survival is monitored by daily palpation of the beating donor heart through the abdominal wall. Rejection is considered to be complete when heart beat stops. Increases of graft survival are obtained in animals treated with a compound of formula I, II, III or IV or a pharmaceutically acceptable salt or solvate thereof administered orally at a daily dose of 10 to 30 mg/kg bid. In this model, a prolongation of graft survival for 14, 25, 26 days was obtained with Compound A when administered at a dose of 30 mg/kg bid.

In vivo: Graft v. Host Model

Spleen cells ($2x10^7$) from Wistar/F rats are injected subcutaneously into the right hind footpad of (Wistar/F x Fischer 344)F_1 hybrid rats. The left footpad is left untreated. The animals are treated with the test compounds on 4 consecutive days (0-3). The popliteal lymph nodes are removed on day 7, and the weight differences between two corresponding lymph nodes are determined. The results are expressed as the inhibition of lymph node enlargement (given in percent) comparing the lymph node weight differences in the experimental groups to the weight difference between the corresponding lymph nodes from a group of animals left untreated with a test compound. In this assay, an inhibition of 70 to 80% is obtained with compound A when administered at a dose of 30 mg/kg bid.

In vivo: Treatment of Multiple Sclerosis

SJL/J Mouse model of chronic progressive experimental autoimmune encephalomyelitis (EAE)

Immunization: On day 0, female SJL/J mice are immunized (subcutaneous flank injection) with 200 □l inoculum containing 500 □g bovine myelin basic protein (MBP) emulsified in complete Freund's adjuvant (CFA). On day 9, mice are boosted by a second MBP injection and an additional intravenous adjuvant injection consisting of 200 ng *B. pertussis* toxin. A final Pertussis injection is given on day 11.

Most of the MBP-immunized mice exhibit a severe bout of EAE by day 21. This is followed by a recovery phase starting around day 25, during which time mice remain symptom-free

for about 20 days. Subsequently, by days 45-47, approximately 50% of the animals go into the progressive phase of the disease. Therefore, therapeutic treatment with test compounds starts on day 21 when the disease is fully established and continues until day 70, unless stated otherwise. Recombinant mouse interferon beta (INFβ Calbiochem/Biosciences) is dissolved in saline and given by intraperitoneal injection 3x per week. Compounds of the invention, e.g. Compound A, are administered p.o. 5x per week by gavage. Mice in the vehicle control group are MBP-immunized and treated with water.

Each experimental group consists of 10 mice, which are examined daily for clinical EAE symptoms. Disease incidence and the day of EAE onset also are recorded. Clinical grades of EAE are assessed using a scale from 0 to 3. Any disease-related mortality which occurs after starting drug treatment is recorded with a maximum score of 3.

Daily dosages required in practicing the method of the present invention will vary depending upon, for example, the compound used, the host, the mode of administration and the severity of the condition to be treated. A preferred daily dosage range is about from 1 mg to about 1000 mg of active substance as a single dose or in divided doses.

Compounds of formula I, II, III or IV, e.g. of formula Ia, Ib, IIa, or IIIa, or pharmaceutically acceptable salts or solvates thereof may be administered as the sole active ingredient or together with other drugs in immunomodulating regimens e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection. For example, they may be used in combination with a calicineurin inhibitor, e.g. cyclosporin A, ISA Tx247, FK506, ABT-281, ASM 981; an mTOR inhibitor, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578, or a rapalog, e.g. AP23573, AP23464, AP23675, AP23841, TAFA-93, biolimus 7 or biolimus 9 etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; an S1P receptor agonist, e.g. FTY 720 or an analogue thereof; leflunomide or analogs thereof; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or analogs thereof; immunosuppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD 11a/CD18, CD7, CD25, CD27, B7, CD40, CD45, CD58, CD 137, ICOS, CD150 (SLAM), OX40, 4-1BB or their ligands, e.g. CD154; or other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for example designated ATCC 68629) or a mutant thereof, e.g. LEA29Y, or

other adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including LFA-1 antagonists, Selectin antagonists and VLA-4 antagonists.

In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a protein kinase C inhibitor of formula I, II, III or IV, e.g. of formula Ia, Ib, IIa, or IIIa, or a pharmaceutically acceptable salt or solvate thereof, and a second drug substance, said second drug substance being an immunosuppressant or immunomodulatory drug, e.g. as indicated above.

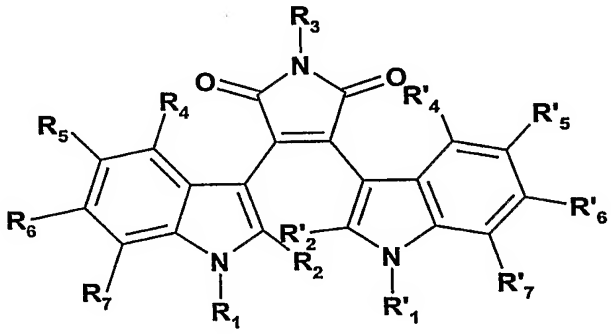
6. A therapeutic combination, e.g. a kit, comprising a) a protein kinase C inhibitor of formula I, II, III or IV, e.g. of formula Ia, Ib, IIa, or IIIa, or a pharmaceutically acceptable salt or solvate thereof, and b) at least one second agent selected from an immunosuppressant and immunomodulatory drug. Component a) and component b) may be used concomitantly or in sequence. The kit may comprise instructions for its administration.

Where a protein kinase C inhibitor of formula I, II, III or IV, e.g. of formula Ia, Ib, IIa, or IIIa, or a pharmaceutically acceptable salt or solvate thereof is administered in conjunction with other immunosuppressant or immunomodulatory drug, e.g. for preventing or treating acute or chronic graft rejection or autoimmune diseases as hereinabove specified, dosages of the co-administered immunosuppressant or immunomodulatory compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a cyclosporine, on the specific drug employed, on the condition being treated and so forth.

CLAIMS

1. Use of a protein kinase C inhibitor of formula I, II, III or IV or a pharmaceutically acceptable salt or solvate thereof in the preparation of a pharmaceutical composition for the treatment and prevention of autoimmune diseases,

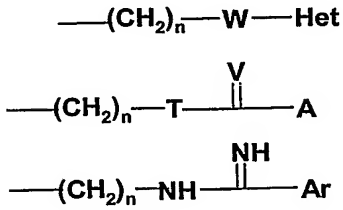
wherein compounds of formula I are



I

wherein

each of R_1 and R'_1, independently, is hydrogen, alkyl, haloalkyl, alkenyl, arylalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, acylaminoalkyl, acyloxyalkyl, cyanoalkyl, amidinoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, or a group of the formula (a), (b) or (c)



(a)

(b)

(c)

wherein Het signifies a heterocyclyl group; W signifies NH, S or a bond; T signifies NH or S; V signifies O, S, NH, or NCN; A signifies alkylthio, amino, monoalkylamino or dialkylamino; Ar signifies aryl;

each of R_2 and R'_2, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, $S(O)C_1$–C_3alkyl, CF_3;

or R_1 and R_2 form together $—(CH_2)_r—X—CH_2—$ wherein r is 1, 2, or 3, and X is CHR_8 or NR_8 wherein R_8 is $(CH_2)_sR_9$ wherein R_9 is hydrogen, hydroxy, alkoxy, amino,

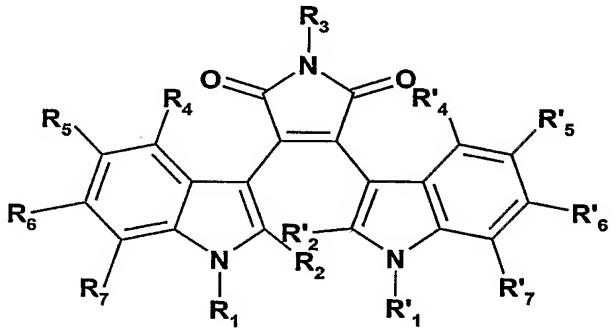
monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl, and s is 0, 1, 2 or 3;

R_3 is hydrogen or CH_3CO;

each of R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7 and R'_7, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, —$COO(C_1–C_3alkyl)$, CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, $C_1–C_3$alkylthio, or $S(O)C_1–C_3$alkyl; and

n is 1, 2, 3, 4, 5 or 6;

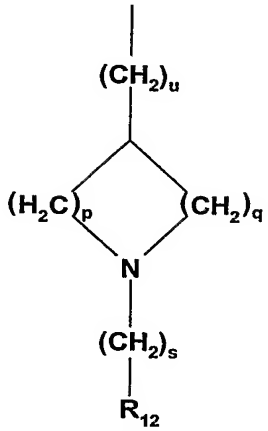
and compounds of formula II are



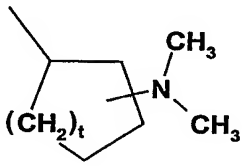
II

wherein

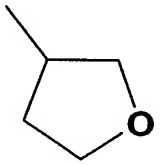
R_1 is a group of formula (d), (e) or (f)



(d)



(e)



(f)

wherein each of p and q independently is 1, 2, 3, or 4;

s is 0, 1, 2 or 3;

t is 1 or 2;

u is 0 or 1; and

R_{12} is hydrogen, alkyl, haloalkyl, cycloalkyl, acetyl, aryl, --CH(aryl)$_2$, amino, monoalkylamino, dialkylamino, guanidino, —C(=N(alkoxycarbonyl))NH(alkyoxy-carbonyl), amidino, hydroxy, carboxy, alkoxycarbonyl or heterocyclyl;

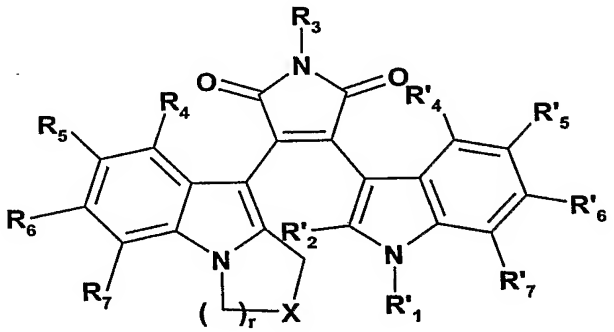
R'_1 is hydrogen, C_{1-4}alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl,

each of R_2 and R'_2, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, S(O)C_1–C_3alkyl, CF_3;

R_3 is hydrogen or CH_3CO—; and

each of R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7 and R'_7, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, --COO(C_1–C_3alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_3alkylthio, or S(O)C_1–C_3alkyl;

and compounds of formula III are



III

wherein

R'_1 is hydrogen, C_1-C_4alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R'_2 is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, S(O)C_1–C_3alkyl, CF_3

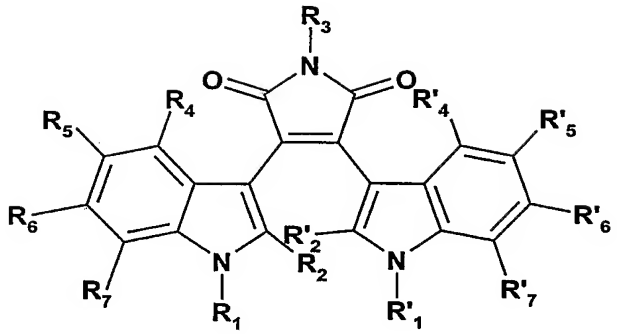
R_3 is hydrogen or CH_3CO—;

each of R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7 and R'_7, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, —COO(C_1–C_3alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_3alkylthio, or S(O)C_1–C_3alkyl;

X is CR_8R_9 wherein R_8 is $(CH_2)_sR_{10}$ wherein R_9 is $(CH_2)_sR_{11}$, each of R_{10} and R_{11}, independently, is hydroxy, alkoxy, carboxy, acyloxy, amino, monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl, and s is 0, 1, 2 or 3; and

r is 1, 2, or 3; and

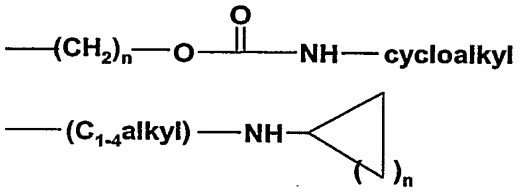
and compounds of formula IV are



IV

wherein

R_1 is alkylglycose residue or a group of formula (g) or (h)



(g)

(h)

wherein n is 1, 2, 3, 4, 5 or 6;

R'_1 is hydrogen, C_1-C_4alkyl, cyclopropylmethyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

each of R_2 and R'_2, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, $S(O)C_1$–C_3alkyl, CF_3;

R_3 is hydrogen or CH_3CO—; and

each of R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7 and R'_7, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, --$COO(C_1$–C_3alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_3alkylthio, or $S(O)C_1$–C_3alkyl.

2. Use according to claim 1 wherein the autoimmune diseases are selected from inflammatory bowel diseases e.g. Crohn's disease and ulcerative colitis; amyotrophic lateral sclerosis; multiple sclerosis; rheumatoid arthritis and hepatitis C.

3. Use of a protein kinase C inhibitor of formula I, II, III or IV or a pharmaceutically acceptable salt or solvate thereof in the preparation of a pharmaceutical composition for the treatment and prevention of organ or tissue transplant rejection and for the prevention of graft-versus-host disease.

4. A pharmaceutical composition for use in the treatment and prevention of organ or tissue transplant rejection and for the prevention of graft-versus-host disease and/or of autoimmune diseases comprising a protein kinase C inhibitor of formula I, II, III or IV or

a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable diluents or carriers therefor.

5. A method for treating or preventing organ or tissue transplant rejection and autoimmune diseases and for preventing graft-versus-host disease in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a protein kinase C inhibitor of formula I, II, III or IV or a pharmaceutically acceptable salt or solvate thereof.

6. Use, composition or method according to any preceding claim wherein the protein kinase C inhibitor is a compound of formula Ia, Ib, IIa, IIIa or a pharmaceutically acceptable salt or solvate thereof.

7. Use, composition or method substantially as hereinbefore disclosed or defined.